UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

OFFICE OF PESTICIDE PROGRAMS
REGISTRATION DIVISION (7505P)

December 29, 2011

MEMORANDUM: IMIDACLOPRID 10%/FLUMETHRIN 4.5% DOG & CAT COLLARS: DOSAGE AND RELEASE RATES OF ACTIVES

Subject:	Name of Pesticide Product:	PNRI427 INSECTICIDE
	EPA Reg. No. /File Symbol:	11556-RLL
	DP Barcode:	DP 392118
	Decision No.:	440307
	Action Code:	RI10.0
	PC Code:	036007 (Flumethrin: 4.5%)
		129099 (Imidacloprid: 10.0%)

From: Byron T. Backus, Ph.D., Toxicologist
Technical Review Branch
Registration Division (7505P)

Byron T. Backus
12/29/2011
M Backus, Ph.D.

To: BeWanda Alexander/Richard Gebken RM 10
Insecticide Branch
Registration Division (7505P)

Registrant: BAYER HEALTHCARE LLC

FORMULATION FROM LABEL:

Active Ingredient(s):	by wt.
036007 Flumethrin	4.5%
129099 Imidacloprid	10.0%
Other Ingredient(s):	85.5%
TOTAL	100.0%

Action Requested: The Risk Manager requests a review of MRID 482401-40, a 117-page document summarizing dosages and release rates of imidacloprid and flumethrin from a number of cat and dog collar studies.

COMMENTS AND RECOMMENDATIONS:

The following is the executive summary for the review compilation in MRID 48240140:

The material in MRID 48240140 represents the compilation of release rates in a series of studies of the two active ingredients from cat and dog collars containing ~10% Imidacloprid and ~4.5% Flumethrin. Collars were weighed, then worn by cats or dogs for varying periods of time, after which they were weighed and analyzed for content of the two active ingredients.

The dosage rates from a ~10 g cat collar containing ~10% Imidacloprid and ~4.5% Flumethrin were the following:

Short-term (28-91 day) Cat & Kitten Studies: Imidacloprid: Mean dosage rate = 1.88 mg/kg/day (range: 0.71-3.72 mg/kg/day). Flumethrin: Mean dosage rate = 0.19 mg/kg/day (range: 0.05-0.44 mg/kg/day).

Long-term (238-245 day) Cat Studies: Imidacloprid: Mean dosage rate = 0.46 mg/kg/day (range: 0.33-0.60 mg/kg/day). Flumethrin: Mean dosage rate = 0.088 mg/kg/day (range: 0.06-0.12 mg/kg/day).

The dosage rates from a ~35 g dog collar containing ~10% Imidacloprid and ~4.5% Flumethrin were the following:

Short-term (23-91 day) Dog & Puppy Studies: Imidacloprid: Mean dosage rate = 1.49 mg/kg/day (range: 0.70-2.44 mg/kg/day). Flumethrin: Mean dosage rate = 0.24 mg/kg/day (range: 0.07-0.42 mg/kg/day).

Long-term (238-245 day) Dog Studies: Imidacloprid: Mean dosage rate = 0.42 mg/kg/day (range: 0.33-0.52 mg/kg/day). Flumethrin: Mean dosage rate = 0.12 mg/kg/day (range: 0.09-0.18 mg/kg/day).

This report is classified as acceptable (Non-Guideline). It provides useful information regarding the rates of release of the two active ingredients from a collar containing ~10% Imidacloprid and ~4.5% Flumethrin and the exposure to cats and dogs wearing this collar.

Reviewer: Byron T. Backus, Ph.D. **Date:** December 29, 2011
Risk Manager (EPA): 10

STUDY TYPE: Active Release Rates from Cat & Dog Collars (Non-Guideline)

TEST MATERIAL: Collars containing ~10% Imidacloprid and ~4.5% Flumethrin

CITATION: Stanneck, D. (2010) Dosage of the Imidacloprid 10% Flumethrin 4.5% Collar and Release of the Active Ingredients over Time in Cats and Dogs: Review Compilation. Project Number: 35992, PNR1427. Unpublished study prepared by Bayer HealthCare, LLC. 120 p. June 28, 2010. MRID 48240140.

SPONSOR: Bayer HealthCare, LLC
Animal Health Division
P.O. Box 390
Shawnee Mission, KS 66201-0390

EXECUTIVE SUMMARY:

The material in MRID 48240140 represents the compilation of release rates in a series of studies of the two active ingredients from cat and dog collars containing ~10% Imidacloprid and ~4.5% Flumethrin. Collars were weighed, then worn by cats or dogs for varying periods of time, after which they were weighed and analyzed for content of the two active ingredients.

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Long-term (238-245 day) Dog Studies: Imidacloprid: Mean dosage rate = 0.42 mg/kg/day (range: 0.33-0.52 mg/kg/day). Flumethrin: Mean dosage rate = 0.12 mg/kg/day (range: 0.09-0.18 mg/kg/day).

This report is classified as acceptable (Non-Guideline). It provides useful information regarding the rates of release of the two active ingredients from a collar containing ~10% Imidacloprid and ~4.5% Flumethrin and the exposure to cats and dogs wearing this collar.

COMPLIANCE: Signed and dated GLP (noting that this study was not conducted in full compliance with GLP standards), and Data Confidentiality statements were provided. There is no Quality Assurance Statement (presumably because this report represents a review compilation).

RESULTS:

Collars were weighed, then worn by cats or dogs for varying periods of time, after which they were weighed and analyzed for content of the two active ingredients.

Cat studies:

Dosage rates in cat studies (from Table 5 on p. 8 of MRID 48240140):

Study Number	Breed & (body weight range in kg)	Study Duration (Days)	Imidacloprid exposure (mg/kg/day)	Flumethrin exposure (mg/kg/day)
146.266	DSH (3.3-5.1)	2	7.36	0.18
		7	4.73	0.18
		14	3.03	0.23
		28	2.08	0.12
		56	1.44	0.10
		84	1.13	0.18
146.164	DSH (2.3-5.1)	30	3.04	0.44
		238	0.56	0.12
146.303	DSH (3.7-4.7)	238	0.39	0.06
146.159	Mix (2.1-4.7)	60	1.27	0.20
152.152	DSH (2.8-5.3)	61	1.62	0.32
152.150	DSH kittens (0.97-1.26 study day 0)	30	3.72	0.20
		60	1.91	0.14
146.747	DSH (3.6-5.7)	28	0.71	0.05
146.156	DSH (2.8-5.3)	238	0.42	0.07
146.045	DSH (3.8-7.0)	241	0.33	0.10
146.155	DSH (2.7-	240	0.60	0.09

There are two mechanisms by which an active can be released from a collar: 1) Simple wear, and 2) Diffusion from the matrix. An approximation of the amount of an active released from wear can be calculated by: weight loss – (amount of imidacloprid lost + amount of flumethrin loss) = amount of plastic lost. Then: (amount of plastic lost)/[1 – (original percentage of imadocloprid + original percentage of flumethrin)] = total amount lost by wear. Then: (total amount lost by wear) x (original percentage of imadocloprid) = amount of imidacloprid lost by wear , and: (total amount lost by wear) x (original percentage of flumethrin) = amount of flumethrin lost by wear. The table below shows that for the cat collar most of the imidacloprid is released by diffusion (the total amount released by wear is approximately 10-14% for 28 days and about 42% for 240 days), while most of the flumethrin is released by wear (the mean total percentage released by wear in the 5 cat studies below which ran for 238-241 days is 99.46%).

Study Number	Body weight range in kg	Study Duration (Days)	Mean collar weight loss (mg)	Plastic weight loss (mg)	Amount of Imidaclo prid released (mg)	Amount of flumethrin released (mg)	Amount in mg of imidacloprid released by wear and % total	Amount in mg of flumethrin released by wear (% total released)
146.156	3.2-5.4	238	2024.44	1518.97	433.1	72.37	179.64 (41.48)	80.04 (110.6)
146.164	2.56-4.22	30	1198.75	860.75	295.58	42.43	100.67 (34.06)	45.30 (106.8)
	2.28-5.14	240	2160.0	1634.56	435.3	90.14	191.18 (43.92)	86.03 (95.44)
146.159	2.4-4.7	60	907.33	634.99	235.60	36.74	72.61 (30.82)	33.34 (90.75)
146.303	3.7-4.7	238	1798.75	1340.35	394.45	63.95	158.52 (40.19)	70.63 (110.44)
146.747	3.6-5.7	28	458.75	239.71	205.34	13.7	27.38 (13.33)	12.29 (89.73)
146.266	3.5-4.1	2	33.33	N.V.	54.67	1.53	N.C.	N.C.
	3.4-5.1	7	133.33	16.36	109.0	7.97	1.93 (1.77)	0.86 (10.82)
	3.4-5.1	14	266.67	103.57	149.5	13.60	12.25 (8.19)	5.46 (40.13)
	3.4-5.1	28	366.67	160.01	195.53	11.13	18.92 (9.68)	8.43 (75.75)
	3.5-5.1	56	633.33	344.69	266.87	21.77	40.77 (15.28)	18.16 (83.43)
	3.3-3.7	84	1000.00	648.2	312.4	39.40	76.66 (24.54)	34.16 (86.69)
146.045	4.6-6.0	241	2197.0	1656.37	411.21	129.42	195.89 (47.64)	87.28 (67.44)
146.155	2.5-3.6	240	1804.0	1334.52	407.48	62.00	157.83 (38.73)	70.32 (113.42)
146.100	2.38-5.8	226[a]	1502.5[a]	1294.77[a]	177.54[a]	30.19[a]	33.98 (19.14)	30.59 (101.31)
	2.58-3.36	226[b]	1696.25[b]	1315.76[b]	349.89[b]	30.60[b]	70.93 (20.27)	31.92 (104.31
	2.28-4.36	226[c]	1725.0[c]	1402.13[c]	297.44[c]	25.43[c]	159.79 (53.72)	35.95 (141.37)

Data calculated from information (Tables) on p. 36, 37, 38, 39, 40, 41, 42

[a]Collar supposedly contained 2.5% Imidacloprid and 2.25% Flumethrin and this reviewer's calculations above are based on that composition; however, column 6 of the Table on p. 44 of MRID 48240140 indicates the collar contained 10.1% Imidacloprid and column 7 indicates it contained 4.5% Flumethrin.

[b]Collar supposedly contained 5.0% Imidacloprid and 2.25% Flumethrin and this reviewer's calculations above are based on that composition; however, column 6 of the Table on p. 44 of MRID 48240140 indicates the collar contained 10.1% Imidacloprid and column 7 indicates it contained 4.5% Flumethrin.

[c]Collar supposedly contained 10.0% Imidacloprid and 2.25% Flumethrin and this reviewer's calculations above are based on that composition; however, column 6 of the Table on p. 44 of MRID 48240140 indicates the collar contained 10.1% imidacloprid and column 7 indicates it contained 4.5% Flumethrin.

Dog studies:

Dosage rates in dog studies (from Table 6 on p. 8 of MRID 48240140):

Study Number	Breed & (body weight range in kg)	Study Duration (Days)	Imidacloprid exposure (mg/kg/day)	Flumethrin exposure (mg/kg/day)
146.165	Mongrel (11.6-19.4)	30	1.62	0.20
		238	0.33	0.11
146.306	Beagle (9.4-13.6)	238	0.52	0.18
146.161	Mix (8.4-20.2)	60	0.89	0.07
152.151	Beagle (8.7-13.4)	60	1.37	0.15
152.149	Beagle puppies (1.5-2.9 on study day 0)	23	2.44	0.36
		30	2.21	0.42
		60	0.97	0.28
146.737	Beagle (8.7-11.7)	28	2.25	0.20
146.158	Beagle (8.8-12.8)	245	0.52	0.11
146.390	Beagle (6.6-20.4)	240	0.35	0.09
146.592	Beagle (8.3-13.5)	240	0.37	0.13
146.269	Mongrel (7.1-21.5)	90	0.70	0.32
146.607	Beagle (10.0-13.1)	91	0.97	0.18

The table below shows that for the dog collar most of the imidacloprid is released by diffusion (the total amount released by wear is approximately 8-22% for 28-30 days and about 29-61.5%, with a mean of ~44% for 238-245 days), while most of the flumethrin is released by wear (the mean total percentage released by wear in the 5 dog collar studies below which ran for 238-245 days was 64.4%).

Study Number	Body weight range in kg)	Study Duration (Days)	Mean collar weight loss (mg)	Plastic weight loss (mg)	Amount of Imidaclo prid released (mg)	Amount of flumethrin released (mg)	Amount in mg of imidacloprid released from wear and % total	Amount in mg of flumethrin released from wear (% total released)
146.164	(11.6-19.4)	30	2145.7	1342.5	715.74	87.49	155.26 (21.69)	70.57 (80.66)
		240	6921.4	5155.95	1310.19	455.26	596.31 (45.51)	271.05 (59.54)
146.158	(8.8-12.8)	245	5136.0	3481.85	1358.7	295.45	406.76 (29.94)	178.97 (60.58)
146.306	(9.4-13.6)	238	6238.8	4458.65	1321.25	458.9	520.87 (39.42)	229.18 (49.94)
146.362/ 146.607	(10.0-13.1)	91	3498.3	2319.43	998.3	180.57	268.25 (26.87)	104.37 (57.8)
146.737	(9.1-11.0)	28	1142.5	445.99	640.61	55.9	51.58 (8.05)	23.45 (41.95)
146.390	(10.4-18.2)	240	5718.0	4297.67	1126.98	303.35	500.90 (44.45)	220.39 (72.65)
146.269	(7.22-21.48)	90	3696.25#	2621.89	796.3	278.06	303.23 (38.08)	137.83 (49.57)
146.161	(10.36-17.56)	60	1633.75	797.53	797.61	38.61	92.24 (11.56)	41.93 (108.59)
146.592	(8.3-13.5)	240	6467.14	5156.91	969.07	341.16	596.42 (61.5)	271.10 (79.46)

Data calculated from information (Tables) on p. 45, 46, 47, 48, 49, 50, 51, 52, and 53.
#No weight loss reported for collar from one dog (CC0CE2); data from this dog not included in calculations by the EPA reviewer.

For the dog studies that ranged from 238-245 days the mean collar weight loss was 6096.27 (range: 5136.0-6921.4) mg; the mean plastic (matrix) weight loss was 4510.21 (range: 3481.85-5156.91) mg; the mean total amount of imidacloprid released per collar was 1217.24 (range: 969.07-1358.7) mg; and the mean total amount of flumethrin released per collar was 370.82 (range: 295.45-458.9) mg. The approximate amount of imidacloprid released per collar from wear was 524.25 (range: 406.76-596.42) mg and the approximate amount of flumethrin released per collar from wear was 234.14 (range: 178.97-271.1) mg.

The following summarizes the dosages given in Tables 5 and 6 on p. 8 of MRID 48240140:

Short-Term (28-91 day) Cat & Kitten Studies:	Imidacloprid exposure (mg/kg/day): 2.08, 1.44, 1.13, 3.04, 1.27, 1.62, 3.72*, 1.91*, 0.71 **[Mean = 1.88]**	Flumethrin exposure (mg/kg/day): 0.12, 0.10, 0.18, 0.44, 0.20, 0.32, 0.20*, 0.14*, 0.05 **[Mean = 0.19]**
Long-Term (238-245 day) Cat Studies:	Imidacloprid exposure (mg/kg/day): 0.56, 0.39, 0.42, 0.33, 0.60 **[Mean = 0.46]**	Flumethrin exposure (mg/kg/day): 0.12, 0.06, 0.07, 0.10, 0.09 **[Mean = 0.088]**
Short-Term (23-91 day) Dog & Puppy Studies:	Imidacloprid exposure (mg/kg/day): 1.62, 0.89, 1.37, 2.44**, 2.21**, 0.97**, 2.25, 0.70, 0.97 **[Mean = 1.49]**	Flumethrin exposure (mg/kg/day): 0.20, 0.07, 0.15, 0.36**, 0.42**, 0.28**, 0.20, 0.32, 0.18 **[Mean = 0.24]**
Long-Term (238-245 day) Dog Studies:	Imidacloprid exposure (mg/kg/dau): 0.33, 0.52, 0.52, 0.35, 0.37 **[Mean = 0.42]**	Flumethrin exposure (mg/kg/day): 0.11, 0.18, 0.11, 0.09, 0.13 **[Mean = 0.12]**

*Kitten study
**Puppy study

Reviewer's Conclusions:

The dosage rates from a ~10 g cat collar containing ~10% Imidacloprid and ~4.5% Flumethrin were the following:

Short-term (28-91 day) Cat & Kitten Studies: Imidacloprid: Mean dosage rate = 1.88 mg/kg/day (range: 0.71-3.72 mg/kg/day). Flumethrin: Mean dosage rate = 0.19 mg/kg/day (range: 0.05-0.44 mg/kg/day).

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This report is classified as acceptable (Non-Guideline). It provides useful information regarding the rates of release of the two active ingredients from a collar containing ~10% Imidacloprid and ~4.5% Flumethrin and the exposure to cats and dogs wearing this collar.

ACUTE TOX ONE-LINERS:

1. **DP BARCODE:** 392118				
2. **PC CODES:** 129099 (Imidacloprid); 036007 (Flumethrin)				
3. **CURRENT DATE:** December 29, 2011				
4. **TEST MATERIAL:** Dog & Cat Collars containing ~10% Imidacloprid & ~4.5% Flumethrin				
Study/Species/Lab Study # / Date	**MRID**	**Results**	**Tox. Cat.**	**Core Grade**
Dosages & release rates of actives (review compilation)/cats & dogs/ Bayer Animal Health, Monheim, Germany/PNR 1427/June 28, 2010	48240140	**Short-term (28-91 day) Cat & Kitten Studies:** Imidacloprid: Mean dosage rate = 1.88 mg/kg/day (range: 0.71-3.72 mg/kg/day). Flumethrin: Mean dosage rate = 0.19 mg/kg/day (range: 0.05-0.44 mg/kg/day). **Long-term (238-245 day) Cat Studies:** Imidacloprid: Mean dosage rate = 0.46 mg/kg/day (range: 0.33-0.60 mg/kg/day). Flumethrin: Mean dosage rate = 0.088 mg/kg/day (range: 0.06-0.12 mg/kg/day). The dosage rates from a ~35 g dog collar containing ~10% Imidacloprid and ~4.5% Flumethrin were the following: **Short-term (23-91 day) Dog & Puppy Studies:** Imidacloprid: Mean dosage rate = 1.49 mg/kg/day (range: 0.70-2.44 mg/kg/day). Flumethrin: Mean dosage rate = 0.24 mg/kg/day (range: 0.07-0.42 mg/kg/day). **Long-term (238-245 day) Dog Studies:** Imidacloprid: Mean dosage rate = 0.42 mg/kg/day (range: 0.33-0.52 mg/kg/day). Flumethrin: Mean dosage rate = 0.12 mg/kg/day (range: 0.09-0.18 mg/kg/day).	n/a	A (non-Guideline)

Core Grade Key: A = Acceptable, S = Supplementary, U = Unacceptable, W = Waived